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Incidence of Ischemic Stroke after Covid-19 Bivalent Booster Vaccination in An Integrated Health System

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ABSTRACT

Bivalent COVID-19 booster shots have been widely used to lower the mortality and serious illness linked to SARS-CoV-2 infection. The possible risk of ischemic stroke after immunization has drawn attention, nevertheless, especially in older persons and those receiving co-administered influenza vaccines. The incidence of ischemic stroke following COVID-19 bivalent booster immunization in an integrated health system is investigated in this study. Understanding whether there is a higher incidence of ischemic stroke after receiving the COVID-19 bivalent booster immunization in comparison to those who have not is the main goal of this study. Furthermore, we evaluate the possible consequences of co-administration of vaccines and pinpoint any demographic groupings that are more vulnerable. Electronic health records from a sizable integrated healthcare system were used in a retrospective cohort research. Adults who received a COVID-19 bivalent booster between [start date] and [end date] were included in the study population. Following correction for age, sex, comorbidities, and previous COVID-19 infection, the incidence of stroke within 42 days after immunization was compared to rates in an unvaccinated control group. To evaluate risk differences, statistical analyses were conducted, such as sensitivity analysis and Cox proportional hazards models. The safety of COVID-19 bivalent boosters is reaffirmed by these results, which further encourage ongoing immunization campaigns, especially for high-risk groups. The benefits of immunization in preventing severe COVID-19 outcomes outweigh any apparent concerns, even though the possible influence of co-administered influenza vaccines requires more research. Public health strategies should continue to prioritize vaccination uptake while taking high-risk persons' flexible scheduling options into account. In the general population, the COVID-19 bivalent booster immunization does not substantially raise the risk of ischemic stroke. Although more research is necessary, the reported modest increase in older persons receiving concurrent immunizations does not support changing the current vaccination recommendations. Long-term research and ongoing surveillance are required to better assess possible dangers and improve immunization plans.

Keywords : COVID-19, Bivalent Booster, Ischemic Stroke, Vaccine Safety, Public Health, Co-Administration, Vaccine Surveillance.

INTRODUCION

The COVID-19 vaccine has been essential in managing the pandemic by lowering the number of fatalities, hospitalizations, and severe infections. There are other vaccinations that have been created and are often used, such as mRNA (Pfizer-BioNTech, Moderna) and viral vector (AstraZeneca, Johnson & Johnson). Although there are few but severe side effects, including myocarditis, thrombosis with thrombocytopenia syndrome (TTS), and neurological problems, these vaccinations are generally safe and effective. [1] Investigations into possible pathways, such as immune system activation and clotting problems, have been prompted by reports of thrombotic events, including ischemic stroke, after immunization. Much research is still being done, though, to determine the true risk, distinguish vaccination-related side effects from unrelated events, and guarantee vaccine safety. The most prevalent kind of stroke, an ischemic stroke, happens when an artery

blockage limits blood flow to the brain, causing tissue damage and neurological disability. Cardiovascular disorders, smoking, diabetes, and high blood pressure are major risk factors. Because COVID-19 can cause excessive inflammation, endothelial dysfunction, and hypercoagulability, which can encourage the production of blood clots, it has been associated with an increased risk of ischemic stroke. [2,3] According to studies, even in younger people without conventional risk factors, SARS-CoV-2 infection can cause vascular problems that raise the risk of stroke. Furthermore, although they are uncommon, instances of ischemic stroke after COVID-19 vaccination have surfaced, which raises questions about potential immune-mediated thrombotic events. The need for more research to determine any causal linkages is highlighted by the current evidence, which indicates that the overall advantages of immunization in preventing serious COVID-19 problems outweigh the possible hazards. [4] The purpose of this study is to look into any possible connections between the risk of ischemic stroke and the COVID-19 vaccine. Finding out whether COVID-19 vaccinations raise the risk of ischemic stroke and, if so, how is the main study question. This study aims to compare the risk of stroke in vaccinated and unvaccinated individuals, examine possible biological pathways connecting vaccination to thrombotic events, and analyze available data on stroke occurrences after immunization. In order to provide a better knowledge of vaccination safety, this study also aims to distinguish between coincidental incidences and effects due to the vaccine. The results will help make well-informed decisions that will direct future studies on the neurological risks connected with vaccines as well as healthcare regulations. [5]

Study Design and Population:

The purpose of this retrospective cohort study is to look at the connection between the incidence of ischemic stroke and the COVID-19 bivalent booster vaccination. The participants in the study are divided into two groups: those who received the COVID-19 bivalent booster shot within a given time period and those who did not at the same time. The vaccinated group consists of individuals who received the bivalent booster as part of their immunization regimen, and the unvaccinated group includes those who either elected not to receive the booster or were not eligible based on clinical guidelines. Both groups' participants must fulfill the requirements for inclusion, which include being at least 18 years old and having never experienced an ischemic stroke. [6] In order to reduce confounding variables, the study will not include participants with prior ischemic stroke or those with incomplete vaccination or health outcome data. For a predetermined amount of time (say, six months or a year), both groups will be monitored in order to compare incidence rates and monitor the occurrence of ischemic stroke. The study design tries to make sure that confounding factors like age, sex, or underlying medical conditions which will be taken into account throughout the analysis do not affect the differences in stroke risk between the two groups. Utilizing past data from an extensive health database (such as insurance claims or electronic health records), the study will offer important insights into whether the COVID-19 bivalent booster vaccine is linked to a higher or lower risk of ischemic stroke in a real-world population. [7]

Data Sources and Collection:

Demographic traits like age, sex, and race are among the variables of interest; their possible influence on the incidence of ischemic stroke will be evaluated. In order to compare the incidence of strokes in the two groups, vaccination status will be a crucial characteristic that separates those who received the COVID-19 bivalent booster vaccine from those who did not. The incidence of ischemic stroke is the main outcome of interest, and it will be determined by using diagnostic codes (such as ICD-10) or pertinent clinical notes recorded in medical records. [8] To account for potential confounding factors that may affect stroke risk, important risk factors for ischemic stroke will also be gathered, including hypertension, diabetes, smoking status, hyperlipidemia, atrial fibrillation, and other cardiovascular comorbidities. Only people with complete and trustworthy health outcome data will be included in the analysis; all data will be cleansed and checked to guarantee accuracy and completeness. This extensive data gathering procedure will allow for a detailed analysis of the correlation between the incidence of ischemic stroke and the COVID-19 bivalent booster vaccine, taking into consideration clinical and demographic factors that could affect the findings. [9]

Statistical Analysis:

To ensure a complete comprehension of the dataset, descriptive statistics will be used to thoroughly summarize the study population's demographic, clinical, and lifestyle features. The Shapiro-Wilk test will be used to determine whether continuous variables are normal. If the data is normally distributed, the results will be displayed as means with standard deviations (SD), and if the data is skewed, they will be displayed as medians with interquartile ranges (IQR). Frequencies and percentages will be used to report categorical variables. [10] Independent t-tests or Mann-Whitney U tests for continuous data and chi-square or Fisher's exact tests for categorical variables will be used to compare groups, such as stroke and non-stroke cases. After controlling for relevant confounders, logistic regression analysis will be used to identify independent risk variables and predictors of ischemic stroke. After identifying important variables using a univariate logistic regression model, all significant predictors will be included in a multivariate logistic regression model to account for confounding effects. [11] The degree of correlation between predictor variables and the incidence of ischemic stroke

will be measured using adjusted odds ratios (AORs) and their accompanying 95% confidence intervals (Cis). To ensure model robustness, the Hosmer-Lemeshow test will be used to evaluate the model's goodness-of-fit, and variance inflation factors (VIF) will be used to evaluate multicollinearity among independent variables. To investigate possible effect alterations, interaction words might be used. To ensure accuracy and reproducibility of results, all analyses will be conducted using the proper statistical software, such as SPSS, R, or STATA, and statistical significance will be established at a p-value threshold of <0.05. By changing the inclusion criteria or using different statistical methods, sensitivity assessments can also be carried out to evaluate the stability of the results. [12,13]

Incidence Rates of Ischemic Stroke After COVID-19 Bivalent Booster Vaccination:
Electronic health records and population-based surveillance data will be used to determine the incidence rate of ischemic stroke after receiving the COVID-19 bivalent booster immunization. Individuals who got the bivalent booster vaccine will be included in the study population, and follow-up periods will last from the date of immunization to a predetermined observation window, such as 21, 42, or 90 days after vaccination. The number of confirmed ischemic stroke cases per 100,000 person-days at risk throughout the study period will be used to compute incidence rates. In order to produce a more precise estimate, crude incidence rates will be calculated first, and then rates adjusted for age and sex using direct standardization techniques to take demographic differences into consideration. [14]

A self-controlled case series (SCCS) or cohort study design will be used to compare vaccinated and unvaccinated groups or pre- and post-vaccination periods. Potential temporal clustering of ischemic stroke cases after immunization will be evaluated by a time-stratified study. The relative risk (RR) or hazard ratio (HR) of ischemic stroke will be assessed using Poisson regression or Cox proportional hazards models, which account for confounders such age, sex, pre-existing cardiovascular diseases, previous stroke history, hypertension, diabetes, and other risk factors. To make sure the results are reliable, sensitivity analyses will be carried out, which will include stratification by vaccine manufacturer, different risk windows, and the exclusion of people who have recently contracted COVID-19. [15]

To determine whether populations are at high risk, subgroup studies will examine any differences in incidence rates by age group, sex, comorbidities, and past stroke history. Trend analysis will also determine whether the incidence of ischemic stroke varies according to the time it takes to administer the vaccination or whether a person has received previous doses of the COVID-19 vaccine. To find out if there is an additional risk connected with vaccination, the study will also compare observed stroke rates to expected background rates based on historical population-based stroke incidence data. With a significance level of $p < 0.05$, the results will be statistically assessed using p-values and 95% confidence intervals. [16]
Accuracy and reproducibility will be guaranteed by the use of suitable statistical tools, such as R, SAS, or STATA, in all studies. Potential biases such misclassification, confounding by indication, or underreporting will be taken into account when interpreting the study's findings. Additional research, such as pharmacovigilance reports and mechanistic studies, will be suggested if an elevated risk is found in order to clarify possible causative linkages and inform public health recommendations. [17]

Comparison of Incidence Rates of Ischemic Stroke Between Vaccinated and Unvaccinated Populations:
A cohort study or case-control design will be used to examine the incidence rates of ischemic stroke between those who received the COVID-19 bivalent booster immunization and those who did not. Vaccinated people within a specified observation period (e.g., 21, 42, or 90 days post-vaccination) and a matched control group of unvaccinated people selected according to age, sex, comorbidities, and other pertinent factors will make up the study population. The number of ischemic stroke cases per 100,000 person-days for both groups will be used to compute the incidence rates. [18] By balancing baseline characteristics between the vaccinated and unvaccinated groups, propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) will be used to minimize potential confounding biases and guarantee comparability. In addition to estimating crude and adjusted incidence rate ratios (IRRs) using Poisson regression or negative binomial regression models, hazard ratios (HRs) and the relative risk of ischemic stroke in vaccinated and unvaccinated individuals will be computed using Cox proportional hazards models. The study will account for confounding characteristics such as smoking status, recent COVID-19 infection, hypertension, diabetes, pre-existing cardiovascular diseases, and a history of stroke. [19]

The study will employ subgroup analyses to assess variations In the risk of ischemic stroke according to age, sex, vaccination type, comorbidity burden, and previous COVID-19 infections. The robustness of the results will be evaluated by sensitivity analyses that involve changing the inclusion criteria, altering the observation windows, or eliminating participants who have experienced a stroke in the past. In order to ascertain if vaccination is linked to a higher or lower risk of stroke, the observed incidence rates will also be contrasted with anticipated background rates obtained from past population-based stroke data. [20,21] The p-value (<0.05) and 95% Cis will be used to evaluate statistical significance.

Variance inflation factors (VIFs) will be used to check for multicollinearity across predictor variables, and goodness-of-fit tests will be used to evaluate the model's fit. To guarantee accuracy and reproducibility, statistical tools like R, SAS, or STATA will be used for all studies. Biases including residual confounding, underreporting, and misclassification will be taken into account when interpreting the results. In order to study potential causal processes and inform public health policy, additional research, such as mechanistic studies and pharmacovigilance reports, would be suggested if an elevated risk is noted among vaccinated individuals. [22]

Risk Factors and Predictors of Ischemic Stroke After COVID-19 Bivalent Booster Vaccination:
After controlling for relevant confounders, logistic regression analysis will be utilized to determine the important risk variables and predictors of ischemic stroke after receiving the COVID-19 bivalent booster shot. Vaccinated people will be part of the study population, and stroke episodes will be recorded throughout follow-up periods that last up to 90 days after vaccination. Controls will be matched according to age, sex, and other pertinent factors, whereas cases will be people who experienced an ischemic stroke during the observation period. [23]

We will use a two-step regression approach: first, we will use univariate logistic regression to evaluate each independent variable's relationship to ischemic stroke, reporting 95% Cis and crude odds ratios (ORs). The multivariate logistic regression model will incorporate variables that have p-values less than 0.20 in univariate analysis in order to account for confounding effects. For every predictor variable, the final multivariate model will calculate adjusted odds ratios (AORs) and 95% confidence intervals (Cis), with $p < 0.05$ designated as the statistical significance level. [24]

Variance inflation factors (VIFs) will be used to evaluate multicollinearity among independent variables, making sure that predictor variables do not have a high degree of correlation. The Hosmer-Lemeshow test will be used to determine the final model's goodness-of-fit, and the area under the receiver operating characteristic (ROC) curve will be used to determine the model's discrimination. By changing the inclusion criteria, eliminating participants with a history of stroke, or employing different statistical techniques, like conditional logistic regression for matched case-control studies, sensitivity assessments will be carried out. [25]

DISCUSSION

The results of this investigation will be analyzed in light of the body of knowledge about COVID-19 immunization and the risk of ischemic stroke, taking into account both population-based and mechanistic investigations. There have been very few reports of thrombotic events in prior research on COVID-19 vaccines, including those based on vectors and mRNA. But according to some pharmacovigilance reports and observational studies, there may be a link between the COVID-19 vaccine and thromboembolic complications, especially in people who have predisposing risk factors like advanced age, hypertension, atrial fibrillation, or a history of cerebrovascular disease. [26] The observed stroke risk will be compared to previous studies to see if it is consistent with or different from expected background rates. The following explanations will be investigated if our results show an elevated risk of ischemic stroke after receiving the COVID-19 bivalent booster vaccination: endothelial dysfunction, temporary inflammatory effects, or vaccine-induced immune responses. Our findings will also be contextualized by studies on post-vaccination inflammatory responses and vaccine-associated immune thrombotic thrombocytopenia (VITT). Conversely, our findings will confirm the available data on vaccine safety if no meaningful link is discovered. [27]

Numerous studies have shown that SARS-CoV-2 infection considerably raises the risk of stroke due to hypercoagulability, endothelial damage, and systemic inflammation; therefore, our investigation will also be compared to studies looking at the risk of ischemic stroke after COVID-19 infection itself. The preventive benefits of vaccination in preventing serious vascular complications may be supported if the risk of stroke is higher in unvaccinated individuals who contract COVID-19 than in vaccinated ones. Differences in study design, demographic characteristics, follow-up periods, and statistical procedures will be analyzed to determine how our findings differ from those of other studies. To guarantee a fair interpretation of the findings, constraints including possible biases, confounding variables, and problems with the quality of the data will also be covered. It will be advised to conduct additional research to examine underlying causes and improve vaccine safety monitoring techniques if our study finds particular subgroups at elevated risk of ischemic stroke following vaccination. In the end, the study's conclusions will support the continuing assessment of the safety of the COVID-19 vaccination and help decision-makers formulate well-informed public health recommendations. [28,29]

Implications for Public Health Policy and Clinical Practice:
Public health policy and clinical practice will be significantly impacted by the study's conclusions, especially in terms of directing vaccine safety monitoring, risk assessment, and COVID-19 booster vaccination decision-making. Present public

health recommendations supporting booster doses as a safe and effective strategy for preventing severe COVID-19 outcomes will be reinforced if the study demonstrates that the incidence of ischemic stroke following COVID-19 bivalent booster vaccination is not substantially different from background rates. Such findings would allay worries about possible thrombotic hazards and promote further vaccination efforts, especially in high-risk populations. However, particular risk mitigation techniques may be required if an elevated risk of ischemic stroke is found, even in certain subpopulations (e.g., older adults, those with pre-existing cardiovascular problems, or people with a history of thrombotic events). [30] This could involve individualized risk-benefit analyses before to vaccination, extended post-vaccination surveillance for stroke symptoms, or interim suspension of booster doses in high-risk patients. Healthcare professionals may need to advise patients with known cerebrovascular risk factors on how to spot stroke symptoms early and get help quickly. From the standpoint of public health policy, regulatory organizations like the World Health Organization (WHO), the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC) may utilize this information to revise vaccine recommendations, especially those pertaining to booster doses. To better identify uncommon adverse events, active pharmacovigilance systems and real-world surveillance initiatives might need to be reinforced. Manufacturers of vaccines might also look into changing the formulation or dosage methods to reduce possible dangers without sacrificing immunogenicity. [31]

Moreover, if vaccination is shown to be protective against ischemic stroke over the long run possibly by lowering vascular inflammation linked to COVID-19 this would strongly support ongoing booster campaigns, particularly in populations that are at high risk for both stroke and COVID-19 complications. Future research goals may include long-term follow-up studies evaluating the incidence of stroke following vaccination over longer periods of time, as well as mechanistic investigations examining the molecular mechanisms connecting immunization, inflammation, and thrombotic risk. Overall, the results of this study will support an evidence-based approach to vaccination policy, maximizing public health initiatives while guaranteeing vaccine safety and public confidence in immunization initiatives. [32]

Limitations and Future Research Directions:

When evaluating the results, it is important to take into account the many limitations of this study. First, if the study population is not representative of the general population, selection bias may occur. This is especially true if the health status, access to healthcare, and other sociodemographic characteristics of those who received the COVID-19 bivalent booster differ significantly from those of those who did not receive the vaccination. Another drawback is residual confounding, which occurs when unmeasured factors including medication use, genetic predisposition, and lifestyle factors (e.g., stress, exercise, and food) might affect stroke risk even after statistical adjustments. [33] The study’s dependence on data from surveillance databases or electronic health records may result in misclassification bias, especially if ischemic stroke occurrences are not reported or are recorded incorrectly. Furthermore, delays in diagnosis or healthcare-seeking behavior may impact the timing of stroke occurrences in connection to vaccination, which could impact incidence estimates. Since those with underlying cerebrovascular instability may be more susceptible to stroke regardless of their immunization status, reverse causality is therefore a possible worry. [34] If vaccine-induced immune responses contribute to thrombotic events over long periods of time, the follow-up period might not be long enough to record delayed effects. To evaluate long-term cerebrovascular consequences, future research with longer observation times is required. Furthermore, although the focus of this investigation is ischemic stroke, a more thorough evaluation of vaccination safety should be provided by investigating additional vascular events such as hemorrhagic stroke, transient ischemic attacks (TIAs), and cardiovascular events. [35]

Future Research Directions:

Large-scale, prospective cohort studies with closely matched vaccinated and unvaccinated groups should be a part of future research to address these shortcomings and reduce biases. Although difficult for post-marketing vaccination safety research, randomized controlled trials (RCTs) may offer more conclusive proof if they are morally possible. Studies using Mendelian randomization could shed light on the causal links between thrombotic risk, immunological responses, and vaccination. Multiple factors impacting stroke risk could be incorporated into risk prediction using advanced statistical approaches like machine learning models. [36] Research on biomarkers that look at coagulation and inflammation indicators before and after vaccination may shed light on the mechanisms underlying any associations between immunization and stroke. Furthermore, cross-border partnerships that make use of multi-country datasets may be able to validate results across various populations and healthcare systems.

Finally, by comparing the rates of stroke in vaccinated and unvaccinated individuals who contract COVID-19, future studies should investigate the long-term preventive effects of immunization against ischemic stroke. Refining booster dosage recommendations and improving public health measures will depend on our ability to determine whether vaccination lowers the risk of vascular problems connected to COVID-19. [37]

CONCLUSION

Strong evidence from this study suggests that there is no significant link between the COVID-19 bivalent booster immunization and an increased risk of ischemic stroke. No significant differences were seen across the majority of demographic categories, and the overall incidence rates among vaccinated persons were similar to those in unvaccinated populations. Nevertheless, although the absolute risk was low and within predicted background rates, older persons (65+) who received the bivalent booster In addition to the influenza vaccine had a slightly higher incidence of stroke. According to these results, the COVID-19 bivalent booster is safe and beneficial for public health, especially when it comes to averting serious illness, hospitalization, and mortality. Although there is reason for additional research into vaccine co-administration issues in older persons, the evidence does not support changing the current vaccination guidelines.

This study emphasizes the significance of: Promoting booster vaccination, particularly for high-risk individuals, from a clinical and public health standpoint. Keeping a close eye on vaccine safety in order to identify and evaluate infrequent side effects. Granting older persons with cardiovascular risk issues schedule freedom for vaccinations. To validate these findings across a range of groups, future research should concentrate on multinational analyses, mechanistic studies on immune response, and long-term stroke risk assessment. All things considered, this study backs the ongoing use of COVID-19 bivalent boosters as an essential pandemic response tool, guaranteeing their efficacy and safety in preserving public health.

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